

Does step-wise voltage ramping protect the kidney from injury during extracorporeal shockwave lithotripsy? Results of a prospective, randomized trial.

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29 **Abstract**

30 **Background**

31 Renal damage is more frequent with new-generation lithotripters. However, animal
32 studies suggest that voltage ramping minimizes the risk of complications following
33 extracorporeal shock wave lithotripsy (SWL). In the clinical setting, the optimal
34 voltage strategy remains unclear.

35 **Objective**

36 To evaluate whether step-wise voltage ramping can protect the kidney from damage
37 during SWL.

38 **Design, setting and participants**

39 A total of 418 patients with solitary or multiple unilateral kidney stones were
40 randomized to receive SWL with the MODULITH® SLX-F2 lithotripter with either step-
41 wise voltage ramping (n=213) or fixed maximal voltage (n=205).

42 **Intervention:** SWL.

43 **Outcomes measurements and statistical analysis:** Primary outcomes were
44 sonographic evidence of renal hematomas and levels of the urinary markers of renal
45 damage. Secondary outcomes included stone disintegration, stone-free rate, and
46 rates of secondary interventions within 3 months of SWL. Descriptive statistics were
47 used to compare clinical outcomes between the two groups. Logistic regression
48 models were generated to assess predictors of hematomas.

49 **Results and limitations**

50 Significantly fewer hematomas occurred in the “ramping” group than in the “fixed”
51 group (12/213 (5.6%) vs 27/205 (13%), $p=0.008$). The “fixed” group exhibited

significantly higher urinary β 2-microglobulin levels after SWL compared to the “ramping” group ($p=0.02$). Urinary microalbumin levels, stone disintegration, stone-free rate, and rates of secondary interventions did not significantly differ between the two groups. While univariate analysis revealed a higher risk for renal hematomas in patients aged ≥ 70 yrs and in patients with body mass index $>30 \text{ kg/m}^2$, in multivariable analysis the mode of voltage application was the only significant predictor (OR=0.37 [95% CI:0.18-0.77] in favor of voltage ramping). The study was limited by the use of ultrasound to detect hematomas.

Conclusion

In this prospective, randomized study, step-wise voltage ramping during SWL was associated with lesser risk of renal damage compared to fixed maximal voltage. At the same time, treatment effectiveness was not compromised.

Current controlled trials: ISRCTN95762080

Patient summary: Lithotripsy is a noninvasive technique that consists of stone disintegration with ultrasonic energy. In this study, two voltage strategies are compared. The results show that progressive increase of voltage during lithotripsy decreases the risk of renal hematoma while maintaining excellent outcomes.

Introduction

Introduction in the early 1980s of the Dornier HM-3 lithotripter for extracorporeal shockwave lithotripsy (SWL) revolutionized the treatment of urolithiasis [1]. Major urological associations currently recommend SWL as first-line treatment for kidney stones <2cm located in the pelvis, or upper or middle calices [2,3]. In recent years, several new-generation lithotripters have been introduced, many of which are being used in everyday clinical practice. Although SWL is generally considered a safe procedure, it is associated with post-interventional renal hematomas in 0.5%-13% of all cases according to prospective data [4-7]. Severe hematomas can initiate an inflammatory response resulting in scar formation and damage to tubules with subsequent loss of functional renal mass [8].

Against this background, current research is dedicated to improving SWL treatment strategies in order to minimize the risk of hematomas while maintaining or improving clinical effectiveness. Porcine models have shown that step-wise voltage ramping can significantly reduce the extent of renal parenchymal hemorrhagic lesions [9]. To date, clinical evidence has come only from trials with a small number of participants and/or suboptimal study design [10-12]. Notwithstanding their shortcomings, these studies suggest that voltage ramping is safe and may even confer a protective effect compared to fixed voltage treatment. On the other hand, data on the impact of voltage application on clinical effectiveness are conflicting [10-12].

To redress the deficiencies of previous studies, we conducted a well-powered, single-blinded, prospective randomized trial to evaluate the effect of step-wise voltage ramping on renal damage during SWL of kidney stones.

Material and Methods

a) Patients and randomization

From July 2010 to March 2013, a total of 418 patients (296 males and 122 females) ≥ 16 yrs of age requiring elective or emergency SWL were randomized without stratification by a software program to treatment using the MODULITH[®] SLX-F2 lithotripter (Storz Medical AG, Trägerswil, Switzerland) with either step-wise voltage ramping or fixed maximal voltage (Figure 1). Unrestricted randomization was chosen because of the high number of patients to be recruited. Allocation concealment until the intervention was ensured by the use of a password-protected computer database. Inclusion criteria were solitary or multiple unilateral radiopaque kidney stones < 3 cm in diameter, ability to receive neuroaxial regional or general anesthesia, and written informed consent. Exclusion criteria were concurrent ureteral stone and contraindications to SWL according to standard guidelines: pregnancy, uncompensated bleeding diathesis (i.e. anticoagulation or platelet anti-aggregation therapy), and uncontrolled urinary tract infection [2,3]. Patients sent by a referring urologist explicitly to be treated with the Dornier HM-3 lithotripter were also excluded (Figure 1). The study protocol was approved by the Ethics Committee of the Canton Bern, Switzerland (protocol number 089/10).

b) Treatment protocol

All patients received SWL treatment under regional or general anesthesia in order to eliminate pain as a limiting factor and to keep respiratory movements regular **as it is a common practice at our department**. The MODULITH[®] SLX-F2 lithotripter is a third generation electromagnetic lithotripter that uses both inline fluoroscopy and ultrasound to locate the stone. Only the standard focal size (6x28mm) was used for both groups. In the “ramping” group, treatment started with a series of 500 SWs at

level 7 corresponding to 14 kV) followed by 1000 SWs at level 8 (16 kV) and 1000 SWs at level 9 (18 kV). In the “fixed” group, 2500 SWs at level 9 were administered. In both groups treatment was terminated prior to reaching the maximum number of SWs upon documentation of complete fragmentation on x-ray. **Shock wave delivery rate was heart beat triggered [6].** Every SWL treatment was performed by the same technician with more than 25 years of experience, under the supervision and guidance of a specially-trained resident and senior staff member.

c) Follow up

Patients were followed up one day and 3 months after SWL using ultrasound to evaluate the presence of subcapsular or perirenal hematoma, and by kidney, ureter and bladder (KUB) x-ray to categorize the degree of stone disintegration: stone-free, fragments <2mm, fragments 2–5mm, or fragments >5mm. All radiographic images were evaluated by the same blinded reader to minimize interobserver variability. If the patient was classified as stone-free according to KUB x-ray one day after SWL, no further imaging was performed at 3 month follow up. Complications and secondary interventions were prospectively assessed by a blinded study nurse. Urine samples were obtained before and 24 hours after SWL and analyzed for tubular (β 2-microglobulin) and glomerular (microalbumin) damage [13].

d) Outcomes measures

Primary outcomes were evidence of renal damage 24 hours after SWL: 1) incidence of renal hematomas in routine sonography, and 2) elevated levels of β 2-microglobulin and microalbumin in urine. Secondary outcomes were evidence of clinical effectiveness: 1) degree of stone disintegration 3 months after SWL, 2) stone-free rates 3 months after SWL, 3) number of secondary interventions (including re-SWL,

JJ stent placement, percutaneous nephrolithotomy, and ureteroscopy), and 4) complications other than hematomas (e.g. urinary tract infections, renal colic, or steinstrasse) within 3 months of SWL. The severity of complications was graded according to the Dindo-Clavien classification. Stone composition was documented if available.

e) Statistical analysis

SAS 9.1 statistical software (SAS Institute Inc., Cary, North Carolina) was used for statistical analyses. Based on the assumption that the incidence of renal hematomas is 5 % [6] after treatment with fixed maximal voltage and 0.45 % after treatment with voltage ramping and that the drop-out rate is 7% [6], a sample size of 428 patients was required to gain a statistical power of 80% ($\beta=0.2$) using a two-sided test at the significance level of 5% ($\alpha=0.05$). Clinical outcomes were compared using the chi-square test, Fischer's exact test, the Student's t-test, or the Mann-Whitney U-test, as appropriate. Adjusted odds ratio (OR) and 95% confidence intervals (CI) were calculated in univariate and multivariate logistic regression model to test for the effect the mode of voltage application had on the risk of renal hematomas, adjusting for age (<40 yrs, 40-59 yrs, 50-59 yrs, 60-69 yrs, >70 yrs), female gender, body mass index (BMI; continuous), and number of SWs (continuous). A two-sided p value <0.05 was considered statistically-significant.

Results

Patient and stone characteristics are shown in Table 1. Of note, the proportions of stones located in the lower calyx, which usually exhibit lower clearance rates [14], were comparable between the two groups. Furthermore, the mean number of shock waves (SW), mean SW frequency, and mean total voltage applied per patient did not differ between the two groups ($p=0.3$, 0.4 and 0.1 , respectively).

Twenty-four hours after SWL significantly fewer renal hematomas were noted in the “ramping” group than in the “fixed” group (12/213 [5.6%] vs 27/205 [13%] (difference, 7.5 percentage points, 95%CI, 1.9 to 13; $p=0.008$;). All patients with renal hematomas remained hemodynamically stable and were managed conservatively; none of them required blood transfusions. While mean urinary $\beta 2$ -microglobulin levels 24 hours after SWL were significantly higher in the “fixed” group than in the “ramping” group, there was no significant difference in post-SWL urinary microalbumin levels between the 2 groups (Figure 2). Stone-free rates at 3 months (146/198 [74%] “fixed” group vs 148/196 [76%] “ramping” group, difference, 1.8 percentage points, 95%CI, - 6.8 to 10; $p=0.7$), stone disintegration, rates of secondary interventions, and complications other than hematomas did not significantly differ between the two groups (Table 2).

Univariate analysis showed higher risk for renal hematomas in patients aged ≥ 70 yrs (OR=0.15 [95%CI: 0.04-0.64], $p=0.03$) and in patients with BMI >30 kg/m² (OR=0.25 [95%CI: 0.10-0.63]; $p=0.003$) (Figures 3A and 3B). In multivariable analysis, the mode of energy application was the only variable associated with the risk of renal hematomas, which was lower with step-wise ramping (OR=0.37 [95%CI 0.18-0.77], $p=0.008$) (Table 3). Of note, total energy applied to patients with and without renal

189 hematoma did not differ within the two groups (40'995kV vs 40'412kV [$p=0.6$] in the
190 "ramping" group and 42'036kV vs 41'582kV [$p>0.9$] in the "fixed" group).

191 Stone analysis was available in 114/213 (54%) patients in the "ramping" group and in
192 110/205 (54%) patients in the "fixed" group. There was no significant difference in
193 stone composition between the two groups ($p=0.4$) (Supplementary figure).

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Discussion

Since the advent of new-generation lithotripters, the increase in the frequency of renal hematomas associated with their use, most likely due to smaller focal zones and higher peak pressures, has raised concerns among the urological community [15]. Although rarely symptomatic, renal hematomas may have devastating long-term effects [8]. Optimization of energy protocols, therefore, is an area of active research.⁸ The present study, representing the largest prospective, randomized clinical trial investigating the effect of the mode of voltage application, demonstrates a beneficial effect of voltage ramping on renal damage without compromising clinical effectiveness.

Lambert et al previously published a randomized trial comparing voltage ramping and fixed energy during SWL [11]. Although urinary markers for renal damage were routinely collected, the study design did not determine renal hematomas as an outcome and therefore the investigators did not systemically search for them. Moreover, the trial had only 45 patients. Nevertheless, significant changes in microalbumin and β 2-microglobulin levels were documented one week after SWL, suggesting less renal damage with voltage ramping. No changes, however, were seen 24 hours after SWL. These results contrast with our own, as we found that β 2-microglobulin levels (as a marker for tubular damage [13]), but not those of microalbumin (as a marker for glomerular damage [13]), were significantly higher in the “fixed” group 24 hours after SWL. Under the hypothesis that one day may not be enough time for urinary markers of renal damage to be sufficiently expressed in urine, we cannot exclude that higher levels of both urinary β 2-microglobulin and microalbumin would have been detected at a later time point in the “fixed” group **as shown by Lambert et al [11]. However, others could demonstrate that**

microalbumin and β 2-microglobulin were increased 24 hrs after SWL [13, 15, 16]. It could therefore be concluded that power ramping may have a greater protective effect on renal tubules than on glomerules.

The kinetic energy carried by SWs fragment stones mainly through tear and shear forces and cavitation, but they also affect the surrounding renal parenchyma [17]. This may cause tearing of vessels, resulting in subcapsular or perirenal hematoma [17]. Importantly, renal hematomas may lead to parenchymal fibrosis and subsequent functional loss analogous to that produced by blunt renal trauma [8,18]. The mechanisms underlying the protective effect of step-wise voltage ramping are not fully understood. Willis et al demonstrated that low-energy pretreatment of porcine kidneys significantly reduced the size of renal hemorrhagic lesions compared to no pretreatment. The authors hypothesized that low-energy SWs induce some degree of renal vasoconstriction, rendering vessels stiffer and less susceptible to rupture during the application of higher voltages [9]. This hypothesis was later corroborated by studies from the same group demonstrating that pretreatment with low-energy SWs induces early renal vasoconstriction during the application of high-energy SWs. By contrast, vasoconstriction occurred only after SWL if pretreatment was absent [19]. Nevertheless, effectors causing vasoconstriction during SWL are unknown and further research is needed to elucidate the full mechanism behind the renal protective response seen during voltage ramping.

We found that age ≥ 70 yrs constitutes a risk factor for renal hematoma, which agrees with previous data from Dhar et al showing a 1.67-fold increase in the risk of renal hematomas using the MODULITH[®] SLX (Storz) for each 10-year incremental increase in age [20]. Possible reasons for their findings and ours could be increased capillary fragility associated with age and other uncontrolled factors such as intake of

drugs affecting hemostasis (e.g. selective serotonin re-uptake inhibitors) or underlying medical comorbidity. In our study patients with BMI >30 kg/m² suffered renal hematomas more frequently after SWL regardless of SW mode, which was already shown in a recently published retrospective study of 10,887 SWL treatment sessions on 6177 patients [21]. Obesity is a state of chronic systemic inflammation and is characterized by oxidative stress that enhances the vulnerability of the vascular basement membrane which in turn may increase the risk of bleeding during SWL [22,23]. In view of the above findings, we argue that in patients with advanced age and/or high BMI, caution should be exercised during SWL and concomitant treatment of both kidneys should be avoided.

In terms of clinical effectiveness, step-wise voltage ramping performed as well as fixed maximal voltage. *In vitro* and *in vivo* studies have suggested that a progressive increase in voltage during SWL produces greater stone comminution, mainly by maintaining favorable stress wave and cavitation bubble dynamics that lead to constant fragmentation rates [24,25]. In the aforementioned study of Lambert et al, the “ramping” group achieved stone-free rates of 81% (18/22) versus 48% (11/23) in the “fixed” group [11]. The definition of “stone-free” was less stringent than in the present study, as patients with fragments <2mm after a single SWL session were also deemed stone-free. In another small randomized trial, Demerci et al reported similar stone-free rates for voltage ramping and fixed voltage [10]. Unfortunately, those two studies recruited insufficient numbers of patients for definitive conclusions. Moreover, in the study of Demerci et al, patients underwent multiple SWL sessions without this confounding factor being taken into account. Interestingly, Honey et al, comparing immediate versus delayed voltage escalation in 160 patients, showed lower success rates (defined as sand or fragments ≤4mm) for the latter method

[12]. Reasons for this finding, which conflicts with those of other studies, are unclear but they could be related to differences in stone burden, stone composition and location, level of operator experience, ramping protocol, and the type of lithotripter used. Overall, the discrepancy between our study and other studies may be explained by differing definitions of success and differences in sample size. Although well-powered, our study design did not define criteria for clinical effectiveness as a primary outcome, and given the experimental and theoretical background, superior clinical effectiveness for step-wise voltage ramping seems to be plausible.

Our prospective, randomized trial is not without limitations. Renal hematomas were systemically diagnosed by ultrasonography, which may have lower sensitivity and specificity in the diagnosis of renal hematomas than magnetic resonance imaging (MRI) or computed tomography (CT) showing an incidence of renal hematomas after SWL of 15-24% [26-28]. Still, ultrasonography remains an easily accessible and cost-effective imaging modality. Furthermore, the clinical relevance of very small hematomas not seen with ultrasound but only with MRI or CT is questionable.

Another limitation of our study is that the number of total SWs administered at maximal energy (18 kV) was higher in the “fixed” group than in the “ramping” group. It has been shown that renal injury and impairment is greater at higher SW voltages [17]. There was, however, no significant difference in total energy applied per kidney/patient between the two groups. Furthermore, total energy applied to patients with and without post-SWL hematoma did not differ within the two groups. We therefore attribute the protective effect on the kidney to the voltage ramping strategy.

293 **Conclusion**

294 Step-wise voltage ramping during SWL was associated with a lower risk of renal
295 damage compared to fixed maximal voltage SWL without compromising treatment
296 efficacy. Although the optimal ramping-up strategy is not yet defined for each of the
297 lithotripters currently in use, patients with advanced age (≥ 70 yrs) and obesity are at
298 increased risk of post-SWL renal damage and are most likely to benefit from a
299 ramping-up SWL strategy.

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